DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

MAY 14 2002

Submission Tracking Numbers (STN): BL **103666/0 and 103666/1000**
(Replaces Reference Numbers: 96-0660 and 96-0819)

Irene R. Clement
Aventis Pasteur Limited
1755 Steeles Avenue West
Toronto, Ontario M2R 3T4
CANADA

Dear Ms. Clement:

Your Biologics License Application for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), "DAPTACEL™," for the active immunization of infants and toddlers at 2, 4, 6, and 17-20 months of age against diphtheria, tetanus, and pertussis, is approved this date. Aventis Pasteur Limited is hereby authorized to manufacture and prepare Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed for introduction into interstate commerce in the United States.

Under this authorization you are approved to manufacture DAPTACEL™ at your Toronto, Ontario, Canada facility under U.S. License No. 1280. Product will be filled, labeled and packaged at this same facility. Aventis Pasteur, Inc. will distribute packaged DAPTACEL™ in the U.S. In accordance with the approved labeling, your product will bear the tradename DAPTACEL™ and will be marketed in 0.5 mL single dose vials.

The dating period for the final fill of this combination product shall be 30 months from the date of manufacture when stored continuously at 2-8° Celsius. The date of manufacture is defined as the date of the initiation of the earliest valid potency test of the final bulk, regardless of which component of the final bulk is tested first. The dating period for each individual adsorbed bulk intermediate of acellular pertussis antigens shall be ——— from the date of preparation. The dating period for each individual adsorbed bulk intermediate of diphtheria and tetanus toxoids shall be ——— from the date of preparation. Any extension of the dating period will require the submission of supporting data as a Prior Approval Supplement to your Biologics License Application for review and approval. Alternatively, you may submit a comparability protocol for stability to be used in extension of dating as a Prior Approval Supplement to your License Application.

You are requested to submit to the Center for Biologics Evaluation and Research (CBER) samples of each future lot of bulk product together with protocols showing the results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, CBER.

We acknowledge the clinical commitments outlined in your letter of May 13, 2002, as follows:

1. You have agreed to submit a clinical development plan to CBER by March 2003 for a study(ies) to assess the use of DAPTACEL™ as a fifth dose at 4-6 years of age following four previous doses of DAPTACEL™. You have agreed to initiate the study(ies) no later than May 2006.

2. You have agreed to complete the ongoing clinical study, ——— , by December 2003 (defined as the Last Person Out following 180-day safety follow-up) and to perform the serology and safety analysis by August 2004 in order to submit a final clinical report to your existing ——— , by December 2004. You have also agreed to submit a Prior Approval Supplement to revise the DAPTACEL™ package insert to include the data from ——— by March 2005.

3. You have agreed to perform a Phase 4 study in children in the United States in order to assess the impact of Prevnar administration on DAPTACEL™ antigens under protocol ——— You have agreed to submit further protocol revisions, if necessary, within 1 month following each CBER review and to initiate the study within 3 months of CBER protocol approval or by August 1, 2002, whichever is later.

4. You have agreed to initiate a Phase 4 post-marketing study, protocol ———, designed to assess the risks of hypotonic-hyporesponsive episodes, seizures and other possible rare events following DAPTACEL™ and other concomitantly administered vaccines following immunization at 2, 4, 6, and 15-18 months of age. You also commit to submit further protocol revisions within 6 weeks following each CBER review and to initiate the study within 3 months of CBER protocol approval, or by October 1, 2002, whichever is later. You have agreed that you will notify us of any plans to prematurely terminate the study (e.g., study site's decision to use an alternative product). In the event that insufficient data are available from this study (protocol ———) to

assess the risk of seizures, you have agreed to submit a protocol(s) for an additional study(ies) within 6 months from the date of notifying CBER of the intent to terminate the study in order to fulfill this post-marketing commitment.

For the chemistry, manufacturing and controls information, we acknowledge all commitments outlined in your letter of May 13, 2002, including your agreement to submit a final report in August 2002 on the stability testing for DAPTACEL™ single dose lots ———————————— at the conclusion of the 30-month time point. This stability report will include results of container closure integrity testing and preservative effectiveness testing of each lot at expiry.

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling of your Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed may require the submission of a Supplement to your Biologics License Application for review and approval prior to implementation.

It is requested that adverse experience reports for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). According to 21 CFR 600.80(c)(2) [Periodic Adverse Experience Reports], the licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals for the first 3 years following approval. Also as noted in this section, the FDA may require that these reports be submitted at different time intervals. Since your product is categorized as a vaccine, these reports should be submitted to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

Please submit four copies of final printed labeling at the time of use. Two copies of final advertising and promotional materials should be submitted at the time of use with FDA form 2567 to the Advertising and Promotional Labeling Staff. Promotional claims should not be contrary to approved labeling. No comparative claims or claims of superiority over other similar products should be made unless data to support such claims are submitted to and approved by CBER.

Please acknowledge receipt of this letter to the Director, Division of Vaccines and Related Products Applications, HFM-475.

Sincerely yours,

for Steven Masiello
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Karen Midthun, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research